Amendments to the Specification

Please replace the paragraph on page 1, lines 4-8, with the following amended paragraph:

This application is a divisional application of U.S. patent application number 09/827,998 filed April 6, 2001, the entire disclosure of which is hereby incorporated by reference. The present application claims priority to U.S. provisional patent application nos. 60/207,456, filed May 26, 2000, and 60/236,359, filed September 27, 2000, the disclosures of which are incorporated herein by reference in their entireties.

Please replace the paragraph on page 1, lines 10-16, with the following amended paragraph:

The present application includes a Sequence Listing filed on one (1) CD-R disc, provided in duplicate, containing a single file named pto_~~MDhMORF-8~~PB0114.txt, having 349 kilobytes, last modified on ~~April 3, 2001~~September 30, 2003, and recorded September 30, 2003~~April 5, 2001~~. The Sequence Listing contained in said file on said disc is incorporated herein by reference in its entirety.

Please replace the paragraphs on page 7, lines 27-32, with the following amended paragraphs:

~~FIG. 3 presents~~FIGS. 3A – 3J present the nucleotide and predicted amino acid sequences of PAPP-Ea;

~~FIG. 4 presents~~FIGS. 4A – 4I present the nucleotide and predicted amino acid sequences of PAPP-Eb; and

~~FIG. 5 presents~~FIGS. 5A – 5G present the nucleotide and predicted amino acid sequences of PAPP-Ec.

Please replace the paragraph on page 20, lines 14-24, with the following amended paragraph:

~~FIGS. 3, 4, and 5~~FIGS. 3A – 3J, 4A – 4I, and 5A - 5G present the nucleotide sequences of PAPP-Ea, PAPP-Eb, and PAPP-Ec cDNA clones, with predicted amino acid translations; the nucleotide sequences are further presented, respectively, in SEQ ID NOs:1 (full length nucleotide sequence of PAPP-Ea cDNA), 3 (full length amino acid coding sequence of PAPP-Ea), 8 (nucleotide sequence encoding the entirety of PAPP-Eb), 10 (full length amino acid coding sequence of PAPP-Eb), 15 (nucleotide sequence encoding the entirety of PAPP-Ec), and 16 (full length amino acid coding sequence of PAPP-Ec).

Please replace the paragraph on page 21, lines 25-33, with the following amended paragraph:

Accordingly, each of PAPP-Ea, PAPP-Eb, and PAPP-Ec cDNA clones described herein has been deposited in a public repository (American Type Culture Collection, Manassas, Virginia, USA) under accession numbers [[_____]]PTA-3399 (PAPP-Ea), [[_____]]PTA-3400 (PAPP-Eb), [[_____]]PTA-3401 (PAPP-Ec). Any errors in

sequence reported herein can be determined and corrected by sequencing nucleic acids propagated from the deposited clones using standard techniques.

Please replace the paragraph on page 56, lines 15-22, with the following amended paragraph:

In a first such embodiment, the invention provides an isolated nucleic acid comprising (i) the nucleotide sequence of the nucleic acid of ATCC deposit [[_____]]PTA-3399, (ii) the nucleotide sequence of SEQ ID NO:1, or (iii) the complement of (i) or (ii). The ATCC deposit has, and SEQ ID NO:1 presents, the entire cDNA of PAPP-Ea, including the 5' untranslated (UT) region and 3' UT.

Please replace the paragraph on page 57, lines 12-19, with the following amended paragraph:

In another embodiment, the invention provides an isolated nucleic acid comprising (i) the nucleotide sequence of the nucleic acid of ATCC deposit [[_____]]PTA-3400, (ii) the nucleotide sequence of SEQ ID NO:8 or (iii) the complement of (i) or (ii), where the referenced ATCC deposit has, and SEQ ID NO:8 provides, the nucleotide sequence of the entire PAPP-Eb ORF and portions of the 3' UT.

Please replace the paragraph on page 58, lines 9-16, with the following amended paragraph:

In a first such embodiment, the invention provides an isolated nucleic acid comprising (i) the nucleotide sequence of the nucleic acid of ATCC deposit

[[_____]]PTA-3401, (ii) the nucleotide sequence of SEQ ID NO:15, (iii) a degenerate variant of SEQ ID NO:15, or (iv) the complement of (i), (ii) or (iii), where the referenced deposit has, and SEQ ID NO:15 provides, the nucleotide sequence of the PAPP-Ec open reading frame.

Please replace the paragraph on page 92, line 26, through page 93, line 8, with the following amended paragraph:

~~FIGS. 3, 4, and 5~~FIGS. 3A - 3J, 4A - 4I, and 5A - 5G present the predicted amino acid sequences encoded by PAPP-Ea, PAPP-Eb, and PAPP-Ec cDNA clones. The amino acid sequences are further presented, respectively, in SEQ ID Nos: 3 (full length PAPP-Ea isoform), 7 (PAPPE-Ea isoform from aa 1 - 19), 10 (full length PAPP-Eb isoform), 12 (amino acid sequence entirely within the novel exon of PAPP-Eb (aa 1735 - 1762)), 13 (amino acid sequence of PAPP-Eb resulting from the frame shift (aa 1763 - 1770)), 14 (amino acids present uniquely within PappE-b, due to exon insertion followed by frameshift (aa 1735 - 1770)), 16 (full length PAPP-Ec isoform), 18 (20 amino acids centered about deletion of exon 21 in PAPP-Ec (aa 298 - 317)).

Please replace the paragraph on page 115, lines 18-31, with the following amended paragraph:

In a first series of protein embodiments, the invention provides an isolated PAPP-E polypeptide having an amino acid sequence encoded by the cDNA in ATCC Deposit No. [[_____]]PTA-3399, or the amino acid sequence in SEQ ID NO:3, which are full length human PAPP-Ea isoforms. The invention further provides isolated PAPP-E

polypeptides having an amino acid sequence encoded by the cDNA in ATCC Deposit No.[[_____]]PTA-3400, or the amino acid sequence in SEQ ID NO:10, which are full length human PAPP-Eb isoforms. The invention also provides isolated PAPP-E polypeptides having an amino acid sequence encoded by the cDNA in ATCC Deposit No.[[_____]]PTA-3401, or the amino acid sequence in SEQ ID NO:16, which are full length human PAPP-Ec isoforms.

Please replace the paragraph on page 145, lines 20-28, with the following amended paragraph:

The PAPP-Ea cDNA was sequenced on both strands using a MegaBace™ sequencer (Molecular Dynamics, Inc., Sunnyvale, CA, USA). Sequencing both strands provided us with the exact chemical structure of the cDNA, which is shown in ~~FIG. 3~~FIGS. 3A - 3J and further presented in the SEQUENCE LISTING as SEQ ID NO:1, and placed us in actual physical possession of the entire set of single-base incremented fragments of the sequenced clone, starting at the 5' and 3' termini.

Please replace the paragraphs on page 146, line 13, through page 147, line 16, with the following amended paragraph:

The PAPP-Eb and PAPP-Ec cDNAs were sequenced on both strands using a MegaBace™ sequencer (Molecular Dynamics, Inc., Sunnyvale, CA, USA). Sequencing both strands provided us with the exact chemical structure of the PAPP-Eb cDNA, shown in ~~FIG. 4~~FIGS. 4A – 4I and further presented in the SEQUENCE LISTING as SEQ ID NO:8, and of the PAPP-Ec cDNA, shown in ~~FIG. 5~~FIGS. 5A – 5G and further presented

in the SEQUENCE LISTING as SEQ ID NO:10. Sequencing further placed us in actual physical possession of the entire set of single-base incremented fragments of the sequenced clones, starting at the 5' and 3' termini.

PAPP-Ea, PAPP-Eb, and PAPP-Ec cDNAs were deposited at the American Type Culture Collection on [[_____]]May 23, 2001, under accession numbers [[_____]]PTA-3399, [[_____]]PTA-3400, and [[_____]]PTA-3401, respectively.

As shown in ~~FIG. 3~~FIGS. 3A – 3J, the PAPP-Ea cDNA spans 6719 nucleotides and contains an open reading frame from nucleotide 767 through and including nt 6142 (inclusive of termination codon), predicting a protein of 1791 amino acids with a (posttranslationally unmodified) molecular weight of 198.6 kD. The clone appears full length, with the reading frame opening with a methionine and terminating with a stop codon before a 3' poly-A tail.

As further shown in ~~FIGS. 4 and 5~~FIGS. 4A – 4I and 5A – 5G, respectively, splice variants PAPP-Eb and PAPP-Ec are 5461 and 4158 nt, respectively. Because the two clones were obtained using a 5' primer designed to amplify only the PAPP-Ea coding region, the clones lack 5' untranslated region (5' UT); we presume that the 5' UT of these two clones, both of which start with the same exon as PAPP-Ea, should be identical to that for the PAPP-Ea clone. The PAPP-Eb and PAPP-Ec clones encode proteins of 1770 (PAPP-Eb) and 1385 (PAPP-Ec) amino acids, respectively, with predicted (post-translationally unmodified) molecular weights of 196 kD and 152 kD, respectively.

Please replace the paragraph on page 149, line 29, through page 150, line 3, with the following amended paragraph:

As shown in FIG. 2, the PAPP-Ef cDNA includes only a portion of exon 1, and is thereafter identical (with a single nucleotide change) to PAPP-Ea, including all of exons 2 - 20, 22 and 23. The exact start of the PAPP-Ef and PAPP-Ef translations are shown on each of ~~FIGS. 3, 4, and 5~~FIGS. 3A and 3B, 4A, and 5A. We detect only a single nucleotide difference between PAPP-Ea and PAPP-Ef in the region in which they are coextensive.

Please replace the paragraph on page 150, line 28, through page 151, line 2, with the following amended paragraph:

Like PAPP-A, all three novel isoforms have the zinc-binding domain ("zinc") characteristic of metzincin superfamily metalloproteases, defined by the degenerate motif "**HE**XX**H**XX**G**XX**H**", where invariant residues are shown underlined and variable residues are shown as "X". In PAPP-Ea, the longest isoform, the zinc binding domain occurs at residues 733 - 743 with sequence **HE**VG**H**VL**G**LY**H**; the sequence is underlined in ~~FIG. 3~~FIG. 3E.